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Causes of acquired isolated neutropenia in adulthood: a single center study

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ABSTRACT

Aims: Neutropenia, associated with several hereditary and acquired causes, is detected in a significant portion of patients presenting to the hematology outpatient clinic today. We conducted this study since we failed to find any Turkish publication on acquired isolated neutropenia in adults.

Methods: This retrospective study examined data belonging to patients aged 18 years and older who applied to the adult hematology outpatient clinic whose absolute neutrophil count (ANC) was below the normal reference values (≤ 1.5x109/L).

Results: 103 adult patients, 93 women and 10 men, were included in the study. Our study detected the cause of acquired isolated neutropenia as chronic idiopathic neutropenia (CINA) in 39.8% (n=41) of patients, autoimmune diseases in 18.4% (n=19), drugs in 14.6% (n=15), folate deficiency in 13.6% (n=14), infection in 9.7% (n=10), and hematological malignancy in 2.9% (n=3) and cyclic neutropenia in 1% (n=1). 92 patients (89.3%) were found to display mild neutropenia while 9 (8.7%) displayed moderate neutropenia and 2 (2%) displayed severe neutropenia. Interestingly, folate deficiency was detected in 6 of 9 (66.7%) moderately neutropenic patients.

Conclusion: In our study, CINA was determined as the most common cause of acquired isolated neutropenia in adults, while autoimmune neutropenia was the second most common. In addition, the detection of folate deficiency in 6 of 9 patients (66.7%) with moderate neutropenia and the fact that these patients were in the advanced age group [mean 68 (range 62-81)] was a major finding of the study.

Key words: Adult neutropenia, acquired isolated neutropenia, chronic idiopathic neutropenia, folate deficiency, autoimmune neutropenia

INTRODUCTION

Neutropenia is a condition in which the peripheral blood absolute neutrophil count (ANC) determined based on geographic region is more than two standard deviations below the normal mean.[1] It has been known for a long time that a number of hereditary and acquired diseases cause neutropenia, except for the fact that healthy individuals of African descent have lower neutrophil counts than those of European descent.[1] Neutropenia is associated with decreased neutrophil production, increased sequestration or peripheral destruction depending on the etiology. While the causes of hereditary neutropenia include Kostmann syndrome, X-linked agammaglobulinemia, Shwachman–Diamond syndrome, Chédiak–Higashi syndrome, acquired causes mainly include bacterial, fungal and viral infections, vitamin B12 and folic acid deficiency, exposure to drugs and chemical agents, bone marrow infiltration and autoimmune diseases.[2-5] Despite its wide-spectrum etiology, only a few available publications have investigated acquired neutropenia in the adult age group.[6,7] The aim of this study, designed as a single-center study from Turkiye, was to present the causes of acquired isolated neutropenia in adults living in central anatolia to the literature.

METHODS

In this study, we retrospectively evaluated the data of patients aged 18 years and older who applied to the Erciyes University Faculty of Medicine Adult Hematology Outpatient Clinic between 2015 and 2020 and whose neutrophil count was below normal reference values. The study was approved by

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the Kayseri Erciyes University Ethics Committee. Kayseri Erciyes University Faculty of Medicine Ethics Committee (Date:24.06.2020, Decision No: 2020-319). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Demographic and clinical features of the patients were recorded. Furthermore, the use of legal and illegal drugs and patients' diet programs, if any, were recorded. Since the neutrophil count may be affected by ethnicity, only the data of patients from Central Anatolia were included in the study, and the data of refugees from other countries were excluded. We also excluded patients with hereditary neutropenia and a family history of neutropenia from the study. Also, individuals with previous diagnosis of splenomegaly, portal hypertension, anemia or thrombocytopenia were excluded from the study. Available existing tests were recorded using the patient files such as complete blood count (CBC), serum folate, vitamin B12 level, iron and ferritin, total biochemistry, serological exams for hepatitis B and C virus, Cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, adenovirus, parvovirus B19, antinuclear and anti-DNA antibodies and rheumatoid factor, and bone marrow biopsy. Isolated neutropenia was defined as ANC ≤ 1.5 x 109/L, not multiple cytopenias. In addition, according to the ANC count, neutropenia is classified as *mild* (ANC:1-1.5x109/L), *moderate* (ANC: 0.5-1 x 109/L), and *severe* (ANC < 0.5 x 109/L).[8] The infectious, autoimmune and hematological diseases related neutropenia were defined when diagnoses of the diseases were established by specific laboratory exams. Also, drug-induced neutropenia was diagnosed in patients under treatment with drugs associated with idiosyncratic neutropenia, in whom the neutrophil counts reached normal values when the treatment was withdrawn.[9,10] Cyclic neutropenia was characterised by regularly recurring episodes of neutropenia, as described literature.[11,12] Neutropenia lasting at least 3 months and not attributable to drugs or a specific infectious, inflammatory, autoimmune or malignant cause was termed chronic idiopathic neutropenia of adults (CINA).[13]

Statistical Analysis

Descriptive statistics were expressed using mean, standard deviation, median minimum and maximum values. The distribution of variables was measured with the Kolmogorov-Smirnov test. Data analysis was performed using SPSS 26.0 program.

RESULTS

The study population consisted of 103 persons (93 females, 10 males) (Table 1). The median age of the patients was 47 (18-81) years. The mean ANC count was 1.3 ± 0.5 x 109/L. Other blood count parameters were within the normal limits. The detected causes of neutropenia are presented in Table 2. CINA and autoimmune neutropenia were identified in 39.8 and 18.4% (n=41 and 19), respectively, of our cohort of individuals. Their mean ANC counts were 1.3±0.2 x 109/L and 1.2±0.2x109/L, respectively. The autoimmune neutropenia group included 8 patients (7.8%) diagnosed with mixed connective tissue disease, 6 patients (5.8%) with systemic lupus erythematosus, and 5 patients (4.8%) with rheumatoid arthritis. Approximately forty percent of patients presented neutropenia associated with drugs (14.6%, n=15)(mean ANC, 1.2±0.1x109/L), folate deficiency (13.6%, n=14) (mean ANC, 1.1±0.3 x 109/L), and infection (9.7%, n=10) (mean ANC, 1.3±0.7x109/L). The drug-induced neutropenia group included 7 patients (6.8%) with a history of non-steroidal anti-inflammatory drug use (3 diclofenac, 2 ibuprofen, 1 naproxen, 1 etodolac), 6 patients (5.8%) with antibiotic use (4 amoxicillin-clavulanic acid, 2 levofloxacin), and 2 patients (1.9%) with antiepileptic use (1 carbamazepine, 1 sodium valproate). The infection-related neutropenia group included 4 patients (3.9%) with Hepatitis B, 2 patients (1.9%) with Cytomegalovirus and parvo virus B19, and 1 patient (1%) with Epstein-Barr virus and Hepatitis C. The hematological malignancy group, in which 3 patients (2.9%) were diagnosed using bone marrow biopsy, included 2 patients (1.9%) diagnosed with myelodysplastic syndrome (MDS) and 1 patient (1%) with acute myeloid leukemia (AML). Another patient in the group was diagnosed with cyclic neutropenia.

Table 1. Clinical characteristics and blood counts of 103 patients with neutropenia

Paremeters	n	Reference range
Age (years)[a]	47 (18-81)	
Gender (male/female)	10/93	
Hemoglobin (g/dl)[b]	12.5 ± 1.5	12-16
WBC (x109 /L)[b]	4.2± 0.5	4.0-10.5
ANC (x109 /L)[b]	1.3 ± 0.5	2.2-4.8
Lymphocytes (x109 /L)[b]	1.8± 0.4	1.3-2.9
Monocytes (x109 /L) [b]	0.6± 0.2	0.3-0.8
Eosinophils (x109 /L)[b]	0.1± 0.1	0-0.2
Basophils (x109 /L)[b]	0.03± 0.01	0-0.1
Platelets (x109 /L)[b]	211 ± 48.1	130-400

WBC: White blood cell, n:Number, ANC: absolute neutrophil count aMedian (range), bMean ± standard deviation

Table 2. Causes of neutropenia in 103 patients enrolled in study

Neutropenia	n (%)
Chronic idiopathic neutropenia of adults	41 (39.8)
Autoimmune neutropenia	19 (18.4)
Mixed connective tissue disease	8 (7.8)
Systemic lupus erythematosus	6 (5.8)
Rheumatoid arthritis	5 (4.8)
Drug-induced neutropenia	15 (14.6)
Nonsteroidal anti-inflammatory drugs	7 (6.8)
Antibiotics	6 (5.8)
Antiepileptic	2 (1.9)
Folate deficiency	14 (13.6)
Infection-related neutropenia	10 (9.7)
Hepatitis B	4 (3.9)
Cytomegalovirus	2 (1.9)
Parvo B19	2 (1.9)
Epstein-Barr virus	1 (1)
Hepatitis C	1 (1)
Hematological malignancy	3 (2.9)
Myelodsyplastic syndrome	2 (1.9)
Acute myeloid leukemia	1 (1)
Cyclic neutropenia	1 (1)

As shown in the results, 92 (89.3%) of the patients had mild neutropenia, while 9 (8.7%) had moderate and 2 (2%) had severe neutropenia. Two patients with severe neutropenia were

in the drug-induced neutropenia group. One of these patients had a history of 3-month antiepileptic (carbamazepine) use, while the other had a history of 7-month nonsteroidal anti-inflammatory drugs (diclofenac) use. On the other hand, 6 out of 9 (66.7%) moderately neutropenic patients had folate deficiency (≤4 ng/ml), 2 (22.2%) had CINA, and 1(11.1%) had hematological malignancy (AML). The mean age of 14 patients with folate deficiency was 62 (58-74), while the mean age of 6 patients with moderate neutropenia was 68 (62-81) years.

DISCUSSION

In the literature, existing studies mostly focus on the childhood age group in which hereditary diseases, infections and CINA are reported as the major causes.[14] Acquired isolated neutropenias in adults may include a wide range of disorders with variable clinical significance. Although drugs, infections, autoimmune diseases, folate and B12 deficiency are considered as major causes associated with isolated neutropenia in adults, CINA is still considered to be the most common cause today.[11,10,15] During our literature review, we have not encountered an extensive study on the etiology of acquired isolated neutropenia in adulthood in Turkiye. CINA was the most common neutropenia seen in our study, comprising 39.8% (n=41) of the cohort of individuals. CINA is a benign granulocytic disorder characterized by an "unexplained" decrease in the ANC to below the lower limit of the normal distribution for a prolonged period of time. This condition was firstly described by Kyle and Linman in 1968,[16] and its natural history was reviewed some years later by Kyle.[17] There is no history of exposure to irradiation, chemical compounds, or drugs capable of causing neutropenia, or evidence for any underlying disease to which neutropenia might be ascribed, and a genetic predisposition or cyclic fluctuation of neutrophils cannot be demonstrated in these patients.[8] In adult women, CINA are relatively common, with a female to male ratio of about 5:1. In our study, 93 of the patients were female and 10 were male, and all patients with CINA were female. CINA was also seen as a common disorder among apparently healthy persons by Lima et al.[12] and Papadaki et al.[18]

Autoimmune neutropenia (18.4%, n=19) was detected as the second most common cause in our study. Autoimmune neutropenia, caused by neutrophil-specific autoantibodies is a common sign in autoimmune disorders such as systemic lupus erythematosus. In this situation, antineutrophil antibodies can affect neutrophil function causing qualitative abnormalities such as defective response to chemotaxis.[19] As per our results, we identified mixed connective tissue disease as the major cause of autoimmune neutropenia in 8 (7.8%) patients, systemic lupus erythematosus in 6 (5.8%) patients, and rheumatoid arthritis in 5 (4.8%) patients, which is consistent with the literature.[6,5]We found neutropenia associated with drugs 14.6% (n=15) of our patients. In the literature, the incidence of drug-induced neutropenia varies between 2.4-15.4 per million.[11] The pathogenesis of drug-induced neutropenia is a heterogeneous process which is not yet fully understood. In many cases, neutropenia occurs after prolonged drug exposure, resulting in decreased granulocyte production by hypoplastic bone marrow. In other cases repeated, intermittent exposure is implicated. This suggests an immune mediated mechanism, although this hypothesis is not entirely confirmed.[11,20] As per our results, neutropenia-inducing drugs were identified as nonsteroidal anti-inflammatory drugs (3 diclofenac, 2 ibuprofen, 1 naproxen, 1 etodolac) in 7 patients, antibiotics (4 amoxicillin-clavulanic acid, 2 levofloxacin) in 6 patients, and antiepileptics (carbamazepine, sodium valproate) in 2 patients. One of the two patients with severe neutropenia had a history of antiepileptic drug use (carbamazepine for 3 months) and the other had a history of nonsteroidal anti-inflammatory drug use (diclofenac for 7 months). In the study of Andres et al.,[21] antibiotics (49.3%), especially β-lactams and cotrimoxazole, antithyroid drugs (16.7%), neuroleptic and anti-epileptic agents (11.8%), antiviral agents (7.9%), and ticlopidine and acetylsalicylic acid (6.9%) were identified as the main drugs associated with neutropenia.

We found neutropenia associated with folate deficiency 13.6% (n=14) of our patients. Detection of moderate neutropenia in 6 of these 14 patients (42.9%) was considered a significant finding. Folate deficiency associated with nutritional deficiency may cause neutropenia. It is especially of great importance to assess the elderly population in this respect.[8] Different studies report folate deficiency between 6.4% and 9.3% in individuals over 65 years of age.[23] In our study, the mean age of 14 patients with folate deficiency was 62 (58-74), while the mean age of 6 patients with moderate neutropenia was 68 (62-81)years.

We found neutropenia associated with infections 9.7% (n=10) of our patients. As infectious agents, hepatitis B were detected in 4 (3.9%) patients, cytomegalovirus and parvovirus B19 in 2 (1.9%) patients, and Epstein-Barr virus and hepatitis C in 1 (1%) patient. Viral infections can supress bone marrow either directly or via an immune-mediated process.[4] In the study of Andersen et al.,[24] HIV (35.6%), viral hepatitis (16%), cytomegalovirus (4.8%) and Ebstein-Barr virus (10.6%) were reported at higher prevalence among neutropenic patients. Also, there are a few reports of isolated neutropenia caused by viral infections, mainly involving parvovirus B19 and cytomegalovirus.[25,26] Our results are consistent with the literature.

We found neutropenia associated with hematological malignancy 2.9% (n=3) of our patients. Two patients (1.9%) were diagnosed with MDS and one patient (1%) with AML upon bone marrow biopsy. At the onset of acute leukemia in adults, the detection of isolated neutropenia may be considered an important warning in the presence of other blood count values within the normal range.

We found cyclic neutropenia 1% (n=1) of our patients. Cyclic neutropenia has been generally diagnosed in children. Yılmaz et al.[14] investigated the causes of severe neutropenia in the pediatric age group and detected the prevalence of cyclic neutropenia as 13.3%. There is insufficient data on the prevalence of cyclic neutropenia in adults.[27]

Limitations

Our study's limitation might be the small number of patients in all groups. Large-scale multicenter studies are needed to confirm our findings especially in adult patients. Bone marrow biopsy could not be performed in the entire study group.

CONCLUSIONS

Consequently, acquired isolated neutropenia may occur due to a wide variety of causes in adults. The results of this study, which was designed as a single-center study from Türkiye, demonstrate that folate deficiency may be an important cause of neutropenia, especially in the elderly group. Folate deficiency may frequently occur due to nutritional deficiency in elderly individuals. Therefore, folate deficiency should be considered in the differential diagnosis if isolated neutropenia is detected even in the absence of anemia in laboratory tests.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Kayseri Erciyes University Faculty of Medicine Ethics Committee(Date: 24.06.2020, Decision No: 2020-319).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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